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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/445,604	12/07/99	ABATANGELO G	515-4181

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EXAMINER	
STROUP,C	
ART UNIT	**PAPER NUMBER**
1633	4

DATE MAILED: 05/23/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
09/445,604	Abatangelo et al
Examiner	**Group Art Unit**
Stroup, Carrie	1633

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *29-56* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *29-56* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Figures 5-9 are objected to for lack of an image.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 28, 44-46, 50, 51, 54 and 55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's claimed invention is to a biological material comprising endothelial cells, glandular cells, skin adnexa, or germinative cells of hair bulb with a biocompatible, biodegradable three-dimensional matrix comprising at least one hyaluronic acid of an ester of heteroaliphatic series, an autocrosslinked ester of hyaluronic acid wherein esterification occurs with the alcoholic functions of the same polysaccharide chain, a crosslinked ester of hyaluronic acid wherein the carboxylic groups are esterified with polyalcohols of the aliphatic, aromatic, arylaliphatic, cycloaliphatic, heterocyclic series, generating crosslinking by means of spacer chains, a hemiester of succinic acid or a heavy metal salt of the hemiester of succinic acid with hyaluronic acid or with partial or total hyaluronic acid esters, or a

sulfated or N-sulfated hyaluronic acid (claim 29). The claimed invention also includes the use of said material as a support for or use in gene transfection (claims 28, 50, 51) or in scalp or liver tissue transplants or for use in cases of insufficient insulin production (claims 44-46).

The specification fails to provide an enabling disclosure for the use of said material in gene transfection due to the limited teachings on methods of conducting said process. The specification states that the material is to augment ex vivo gene therapy (pg 9, lines 23-26), and then states that:

> "In the application of genetic therapy there is often the problem connected to the fact that cells re-implanted in the same organism do not remain in situ long enough in order to express their action. Culturing the cells on matrix according to the present invention is possible to obtain high proliferation rate and engineered tissues having a complex structure very similar to that of the natural tissue of the organism and they are able to give an efficient surgical workability and can be reimplanted overcoming the problem connected to the cells dispersion." (pg 9, line 27-pg 10, line 1).

The specification provides no additional teaching on the method of conducting cell transfection for cells which are seeded into a hyaluronic matrix. For example, are the cells transfected before or after implantation into the matrix? The specification also fails to disclose potential situations in which the artisan would want a transgene expressed in vitro or how to delay the expression of the transgene until the material is grafted into the skin. Additionally, it is noted that the primary problem in the art of *ex vivo* gene therapy is not that the implanted cells fail to remain "in situ" long enough to provide a therapeutic effect, but rather that the level of transgene expression is too low and unstable and short lived so as to achieve a therapeutic effect. For example, Verma et al (*Nature*, Sept 18, 1997, Vol. 389, pages 239-242) disclose that "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story." (Pg 239, col. 1) And, that "Thus far, the problem (with gene therapy) has been an inability to deliver genes efficiently and to obtain sustained expression." (Pg 239, col 3). Therefore, in light of the unpredictability and technical hurdles facing ex vivo gene

therapy and the failure to overcome such by explicit teachings within the specification on vectors, constructs with promoter and enhancers, methods of transfecting cells during the production of a matrix, etc... the skilled artisan would be required to practice undue experimentation to utilize the claimed material to support gene transfection.

The specification also fails to provide an enabling disclosure for the use of said material comprising liver cells for liver tissue transplants, comprising islet of Langerhans cells for use in cases of insufficient insulin production, or comprising germinative cells of hair bulbs for use in scalp (hair) transplants (claims 44-46). The specification provides an exemplification in which liver cells were isolated from the portal vein and hepatic artery of a pig and seeded on the claimed hyaluronic matrix (HYAFF) in four different culture conditions. The specification then provides the results of cell viability for groups A-D, which does not correlated with groups 1-4 (pg 13). If it is assumed that 1=A, 2=B, ..., then materials which had dermal fibroblasts seeded for 7 days prior to liver cell transplantation had the longest longevity (50 out of 90 by week 8). In addition to the confusion on how to interpret the data, the specification fails to disclose the method of use of said cells in liver tissue transplants. For example, is the matrix with the cells to be implanted in the body, and if so where and does the matrix elicit an immune response that destroys the cells? Likewise, the specification provides and exemplification of islets of Langerhans cells seeded onto the hyaluronic matrix with a confusing table of results, where it is assumed that group C wherein the matrix was cultured for 7 days with fibroblasts before islet seeding resulted in the longest survivability (40 out of 90 by 40 days). Again, the specification does not disclose methods of use of said cells to produce insulin in vivo or ex vivo. Lastly, the specification provides an exemplification in which skin adnexa were seeded onto the matrices 3 days, and 3 and 5 weeks after seeding with human skin fibroblasts, wherein the skin adnexa remained viable for up to 35 days. The specification does not disclose, though, the ability of the skin adnexa to produce hair follicles, or methods of transplanting the cells into the scalp for hair regeneration. Therefore, in light of a disclosure in the specification on methods of using the cells once they have been seeded on the matrix for use in liver transplants, insulin production, and scalp transplants, one of skill

in the art would be required to practice undue experimenation to use the claimed invention such that any therapeutic benefit would occur.

Applicant is advised that should claim 50 be found allowable, claim 51 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 51 is also objected to for being an improper dependent claim because it does not further limit the scope of that which is claimed in claim 50.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 28-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 is indefinite because it depends from cancelled claim 27. It is also indefinite because the absence of an article such as "the" or "a" infront of "Biological material" results in the claim reading on any material comprising any biological substance, therefore the scope of the claim is unclear.

Claims 29, 31-38, and 40-52 are unclear as to the metes and bounds of "an ester of heteroaliphatic series". Does this mean that the carboxyl groups of the hyaluronic acid are esterified, or is this an additional chemical group on the matrix?

Claims 29-56 are unclear as to the metes and bounds of derivative of a sulfated or N-sulfated hyaluronic acid? Does this refer to an alteration of just the sulfonyl groups or to any modification to the matrix?

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 29-32, 35-43, 49, 52, 53, and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soranzo et al (WO 96/33750) in view of Cialdi et al (US Patent 6,027,741) and Dorigatti et al (US Patent 5,520,916).

Applicant's claimed invention is to a biological material comprising endothelial cells and a biocompatible and biodegradable matrix comprising an ester of a hyaluronic acid, wherein part or all of the carboxy functions are esterified with alcohols of the alipathic, aromatic, arylaliphatic, cycloaliphatic and heteroaliphatic series. Said matrix may comprise a sulfated of N-sulfated hyaluronic acid.

Soranzo et al disclose an artificial human skin for use in skin grafts, and methods of making such, comprising a microperforated membrane based on a hyaluronic benzyl ester with 75-100% esterification, such as Hyaff 11, in which keratinocytes are seeded on top of an underlying non-woven tissue of the same hyaluronic ester wherein fibroblasts are seeded and may be co-cultured with the keratinocytes (pg 13-14; claims 1-7, 14-16). Soranzo et al teach that the skin may be used for skin or hair grafts (claim 10) or as a diagnostic device to test in vitro for medicants (claim 9). Soranzo et al does not teach the use of endothelial cells, the use of sulfated hyaluronic acid, or the method of esterifying such.

Dorigatti et al disclose that the non-woven tissue of esterified hyaluronic acids, such as Hyaff 11, is comprised of esters of hyaluronic acid with aliphatic, araliphatic, cycloaliphatic or heterocyclic alcohols and discloses

exemplifications utilizing "partial esters" of 50-100% esterification of carboxylic groups (col. 4, lines 24-31; Examples 1-26).

Cialdi et al disclose the use of sulfated hyaluronic acid and esters, wherein 25-100% of the carboxylic groups are in the form of esters, and the co-culturing of human umbilical vein endothelial cells, isolated via collagenase digestion, in the presence of said sulfated esters resulted in formation of a confluent monolayer within the first 24 hours, whereas the control which lacked the hyaluronic esters reached confluency at day 3 (col 12-13, Example 14; Examples 1-11). Cialdi et al also disclose that the sulfated hyaluronic acid functions like heparin to induce angiogenesis and neo-vascularization in vitro as demonstrated via a cell migration assay (Example 15).

In light of Soranzo, Dorigatti, and Cialdi et al it would have been obvious to one of ordinary skill in the art to generate a biological material by replacing or adding to the keratinocytes in Soranzo's matrix of esters of hyaluronic acid with aliphatic, araliphatic, cycloaliphatic or heterocyclic alcohols with endothelial cells, such as human umbilical veins; and to make the material by isolating the cells via enzymatic digestion with collagenase, to amplify the cells on collagen tissues until confluence is obtained, and then transfer them to a sulfonated hyaluronic ester matrix in the presence of a medium comprising fibroblasts. One would have been motivated to make an human umbilical vein endothelial cell/ sulfonated hyaluronic ester matrix complex to promote vascularization as demonstrated by Cialdi et al, and to do so via the claimed method because it would have been an obvious variation to substitute the co-culturing of endothelial cells with hyaluronic esters as disclosed by Cialdi, with cell transplantation onto a matrix as disclosed by Soranzo. One would have also have motivated to use compositions which comprised keratinocytes to generate tissue for use in surgical procedures of skin or scalp graft or to screen for medicants as disclosed by Soranzo et al .

No claims are currently allowed, although claims 33, 34, 54, and 55 for a biological material comprising islet cells, liver cells, and skin adnexa are free of the prior art of record.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carrie Stroup whose telephone number is (703) 306-5439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached at (703) 308-0294. The fax phone number for this Group is (703) 308-8724.

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